REMARKS

I. Status Of The Claims

Claims 1-5 and 7 are pending.

II. Rejection Of Claims 1-5 and 7 Under 35 U.S.C. §103(a)

Claims 1-5 and 7 stand rejected under 35 U.S.C. §103(a) as being obvious over Nestor et al. (EP 0472 220) ("Nestor") in view of Henke et al (US 5,648,333) ("Henke"). More specifically the Examiner states that

> Nestor et al. (EP 0472 220) teach bradykinin antagonists for treating trauma or a pathological condition induced or mediated by bradykinin, in particular wherein the condition to be treated is a joint degenerative disease such as osteoarthritis (i.e., osteoarthrosis) or rheumatoid arthritis. (e.g., claim 26). The compounds taught by Nestor et al. encompass, within the preferred embodiments, the compound H-(D)-ArgArg-Pro-Pro-Gly-Thia-(L)-Ser-(D)-Tic-Oic-Arg-OH (e.g., claims 1-2 wherein A is H, B= D-Arg, C is Gly, Tis Arg, E is Pro, F is Thi (i.e., Thia), G is Ser, I is D-Tic, J is Oic, K is Arg). The limitation of claim 7: "wherein the administration is carried out by subcutaneous, intraarticular, intraperitoneal or intravenous injection or transdermal administration" is taught, e.g., at page 10, lines 10-58.
>
> Nestor et al. do not teach the specific species H-(D)-Arg-Arg-Pro-Pro-Gly-Thia-Ser-(D)-Tic-Oic-Arg-OH, but do teach the species is encompassed by the formula of claim 2 of Nestor et al. A-(B)m-(C)n-T-E-E-C-F-G-I-J-K, wherein A is H, B is Arg, m is 1, n is 0, T is Arg, E is Pro, C is Gly, F is Thi, G is Ser, I is Tic, J is Oic, K is Arg. Claim 26 teaches the use of such compounds for treating osteoarthritis.
>
> Henke et al. teaches the specific compound H-(D)-Arg-Arg-Pro-Pro-Gly-Thia-Ser(D)-Tic-Oic-Arg-OH (see, e.g., Example 60 and column 17, lines 10-18 and 25-67, claims 1, 12, and especially 27-28 and 30) for the treatment of all pathological states which are mediated, caused or supported by bradykinin and bradykinin-related peptides including arthritis and inflammation (e.g., abstract, column 17, lines 10-17). The limitation of claim 7 is taught, e.g., at column 17, lines 25-67.
>
> It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of treating osteoarthrosis Nestor et al. by using the specific compound H-(D)-Arg-Arg-Pro-Pro-Gly-Thia-Ser-(D)-Tic-Oic-Arg-OH taught by Henke et al. The skilled artisan would have been motivated to do so because Henke et al. and Nestor et al. teach that the compound and family of related compounds treat pathological states which are mediated, caused or supported by bradykinin and bradykinin-related peptides. There would have been a reasonable expectation of success, given that the

> species H-(D)-Arg-Arg-Pro-Pro-Gly-Thia-Ser(D)-Tic-Oic-Arg-OH was encompassed within the preferred embodiments of Nestor et al. to treat degenerative diseases such as osteoarthritis (e.g., claims 2 and 26 of Nestor et al.) and was known to be effective to treat arthritis as taught by Henke et al. Please note that the method taught by Nestor et al. necessarily reads upon the limitation "comprising inhibiting matrix degradation" since the method taught anticipates all the instantly claimed steps of the present invention (i.e., treating osteoarthrosis by administering to the patient a pharmaceutically effective amount of pharmaceutical compositions encompassing claimed compounds). The limitation of claim 7, drawn to different types of administration, is taught, e.g., at column 17, lines 25-67 of Henke et al. and page 10, lines 10-58. (Action page 3-5)

Furthermore, the Examiner stated in response to Applicants' amendment and arguments in their response to the previous rejection that the

> arguments above have been carefully considered but not deemed fully persuasive for the reasons set forth above and because Lerner et al. (cited in Nestor) teach at page 538, column 1, lines 24-39 that even though PGE2 when applied to culture cartilage alone did not affect ^{35}S-sulfate release, however, when PGE2 was applied together with conditioned medium from synovium cultured in the presence of indomethacin, there was a significant increase in the release of ^{35}S-sulfate. Lerner et al. teach that "Further experiments are planned to investigate the possible role of bradykinin in the interaction of synovium and articular cartilage". Therefore Lerner et al. (and hence Nestor) do not teach away from teaching inhibiting cartilaginous matrix degradation upon treating osteoarthritis. The 103 rejection is therefore maintained as above. (Action page 3-5)

Applicants traverse the maintenance of the rejection. Applicants note again that Lerner discloses experimental data showing that bradykinin has no effect on the release of calf articular cartilage proteoglycans in vitro, and the same result when the Lerner investigators used PGE_2. Lerner then references work by Jones by stating that

> PGE_2 applied together with conditioned medium from synovium cultered in the presence of indomethacin resulted in a significant release of ^{35}S-sulfate. (Page 538)

Lerner then states that

> Further experiments are planned to investigate the possible role of bradykinin in the interaction of synovium and articular cartilage. (Page 538)

This disclosure in Lerner does not suggest that the experiments with bradykinin with synovium and articular cartilage would in fact have evidence any effect on cartilage. Furthermore, by the Jones reference referring at page 181 to the "...inconsistency of our results ..." and at page 182 "...explanation for this apparently contradictory result..." shows that there was some issue with the reported results. Lastly the results show nothing with regard to the use of bradykinin, and Lerner clearly shows that bradykinin has no effect on cartilage release Therefor, the teaching of Nestor by reference to Lerner therein does not support the Examiner's assertion that Lerner does not teach against [bradykinin] inhibiting cartilaginous matrix degradation. In view of the aforesaid, Applicants request the reconsideration and withdrawal of the rejection.

III. Rejection Of Claims 1-5 Under Obviousness-Type Double Patenting Rejection

Claims 1-5 also stand rejected under the judicially created doctrine of obviousness-type double patenting over claims 27-28 and 30 of Henke et al, in view of Nestor. Applicants respectfully traverse this rejection.

The cited claims 27-28 and 30 of Henke et al are directed to compositions and methods for treating a variety of specified conditions including arthritis. There is nothing in these claims about the treatment of degenerative joint diseases such as osteoarthrosis, spondyloses or cartilage atrophy, and certainly no discussion of treating them by inhibiting cartilaginous matrix degradation. Although a wide variety of pathological states are included in these claims, and although degenerative joint diseases have been known for many years, yet there is no teaching or claim in Henke et al directed to the treatment of such diseases. The cited claims include a variety of inflammatory diseases, and other diseases which may cause a great deal of pain. However, there is no indication in these claims that the bradykinin inhibitors may be used for the treatment of cartilage matrix degradation associated with degenerative joint diseases.

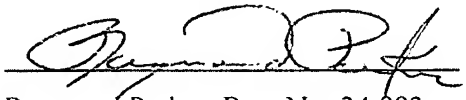
In this rejection, Nestor is cited as a secondary reference to show that such joint diseases are induced or mediated by bradykinin. However, as discussed above, applicants submit that there is no such teaching in Nestor. Therefore, for the reasons discussed here and in the previous part of this response, the Examiner is respectfully requested to reconsider and withdraw this obviousness-type double patenting rejection of the present claims.

For all of the above reasons, it is submitted that all of the claims in the present application are now in condition for allowance, and action to that effect is respectfully requested.

IV. In Conclusion

The Commissioner is hereby authorized to charge the fee required and any additional fees that may be needed to Deposit Account No. 18-1982 in the name of sanofi-aventis Inc.

Respectfully submitted,



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